

# Complements Spurned: Our Experience with Atypical Hemolytic Uremic Syndrome

Vidya S. Nagar, Rudrarpan Chaterjee, Ankita Sood, Basavaraj Sajjan, Aniruddha Kaushik, Sameer V. Vyahalkar<sup>1</sup>

Departments of General Medicine and <sup>1</sup>Nephrology, Grant Medical College and Sir JJ Group of Hospital, Mumbai, Maharashtra, India

## Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare disorder resulting from a dysregulated activation of the alternative pathway of the complement system. It results in significant morbidity and mortality if not diagnosed and treated promptly. It lends itself to myriad renal and extrarenal manifestations, all potentially disabling. Eculizumab, a monoclonal antibody to complement C5 is now the widely accepted norm for treatment. However, in resource-limited settings, plasma exchange if instituted early may be as beneficial. We report a case of aHUS treated with extended plasma exchange with excellent results. Critical care monitoring is essential for the management of the disease in view of a tendency to develop multiple complications. Long-term immunosuppression may be successful in maintaining remission.

**Keywords:** Atypical hemolytic uremic syndrome, complement system, eculizumab, plasma exchange, thrombotic microangiopathy

## INTRODUCTION

Thrombotic microangiopathies result from damage to the endothelium leading to a cascade of thrombosis and resultant anemia, thrombocytopenia, and renal damage. Atypical hemolytic uremic syndrome (aHUS), a rare genetic disorder of this class stems from a rapid inappropriate activation of the complement system, termed “atypical” due to the lack of a triggering event akin to conventional HUS which starts with exposure to the Shiga-like toxin. It has an estimated incidence of 1–2/million, equally distributed in adults and children.<sup>[1,2]</sup> The mortality in pediatric-onset aHUS is reported to be more (6.7%) while adult onset has higher chances of progression to end-stage renal disease.<sup>[2]</sup> Newer therapy such as the complement binding antibody eculizumab is financially unviable at present in the Indian setting.

## CASE REPORT

A 14-year-old male, presented with complaints of sudden reddish discoloration of urine 5 days back followed by yellowing of eyes and skin, nausea, and vomiting associated with feeds. This was preceded by an episode of high-grade fever. At presentation, his vitals were normal. He was afebrile. Severe pallor, as well as icterus, was present. There was no palpable organomegaly. On routine investigation, he was

anemic (hemoglobin 4.9 g%) with thrombocytopenia (platelets 97,000). Total leukocyte counts were normal. Renal functions were deranged with a serum creatinine of 4.27 and blood urea of 116.8. His total bilirubin was 5.3 with an indirect component of 4.1. Kidney sizes were normal with raised cortical echogenicity and a normal renal Doppler study. Serum lactate dehydrogenase levels were raised at 2944 IU/L. A peripheral blood smear revealed dimorphic anemia with thrombocytopenia with polymorphonuclear leukocytosis with abundant schistocytes and tear drop cells suggestive of hemolytic uremic syndrome with a reticulocyte count of 30%. Urine analysis showed granular and hyaline casts and strongly positive test for hemosiderin. Urine output was adequate. Anti-nuclear antibodies were absent with low complement 3 (C3) and normal C4 levels. Anti-complement factor H (CFH) antibodies were found to be significantly raised at 2043 AU/ml. A diagnosis of aHUS was made. He was initiated on plasma exchange with 7 initial daily cycles and a total of 16 cycles titrated to clinical response. His renal and liver

**Address for correspondence:** Dr. Rudrarpan Chaterjee, Room 416, 300 Resident Doctor's Hostel, JJ Hospital, Byculla, Mumbai - 400 008, Maharashtra, India.  
E-mail: rudi.gmc2009@gmail.com

### Access this article online

Quick Response Code:



Website:  
www.ijccm.org

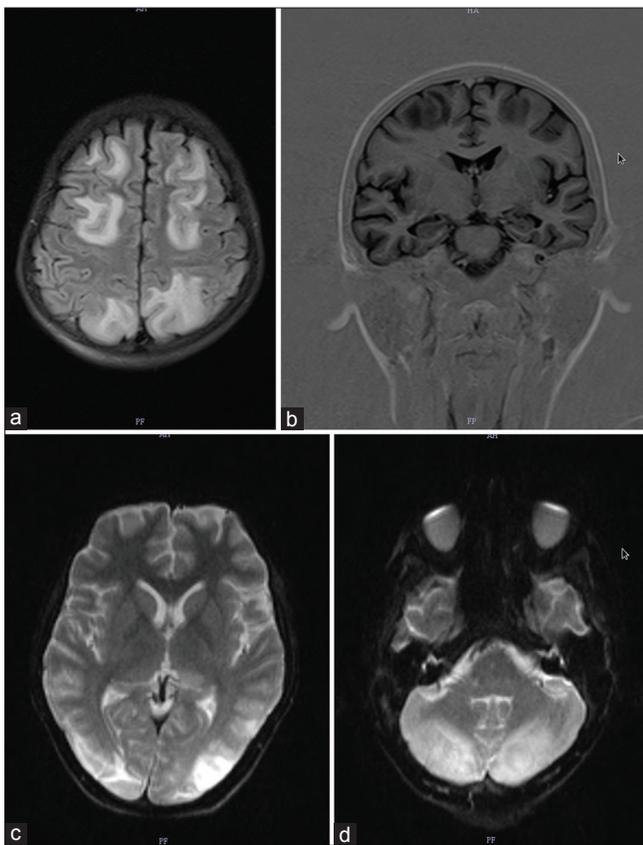
DOI:  
10.4103/ijccm.IJCCM\_341\_16

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Nagar VS, Chaterjee R, Sood A, Sajjan B, Kaushik A, Vyahalkar SV. Complements spurned: Our experience with atypical hemolytic uremic syndrome. Indian J Crit Care Med 2017;21:102-4.

functions normalized by the 12<sup>th</sup> cycle. Anti-CFH antibodies were repeated and found to have decreased to 191.07 AU/ml. Peripheral smear showed a complete absence of schistocytes with urine negative for hemosiderin. He later developed sudden onset severe headache followed by loss of vision progressing to generalized tonic-clonic seizures and status epilepticus. Blood pressure was increased at 200/140 mmHg. He was intubated and later successfully weaned off mechanical ventilation. A magnetic resonance imaging (MRI) brain revealed posterior reversible encephalopathy with altered signal intensity in a subcortical white matter of the bilateral parietal, occipital, posterior temporal lobes and cerebellar hemispheres [Figure 1]. He subsequently developed three more episodes of status epilepticus with posterior reversible encephalopathy. Blood pressure control was achieved using nifedipine, labetalol, and telmisartan. Seizures were controlled on phenytoin, levetiracetam, and clobazam. Severe skin rashes developed almost 2 months into admission: Centripetal in development with mucosal involvement and was diagnosed as Steven–Johnson syndrome [Figure 2]. Phenytoin was withheld and the lesions resolved. He was started on further immunosuppression with steroids and azathioprine and discharged on day 91 of admission in complete clinical and hematological remission.



**Figure 1:** (a) Symmetrical T2 hyperintensities in bilateral parietal lobes. (b) Thermal-infrared images show symmetrical hypointense lesions in bilateral parietal lobes. (c) Fluid-attenuated inversion recovery hyperintensities in occipital lobe typical of posterior reversible encephalopathy. (d) Bilateral symmetrical fluid-attenuated inversion recovery hyperintensities in cerebellum.

## DISCUSSION

aHUS is a thrombotic microangiopathy resulting from mutations in CFH, complement factor I, membrane cofactor protein (CD46), C3, thrombomodulin, CFH-receptor 5, or from autoantibodies to CFH. CFH mutations are the most common affecting 25% cases of aHUS.<sup>[3]</sup> Autoantibodies to CFH reported in 4%–14% of all cases, however, are much more common in cases with early onset of disease and are present in up to 25% of such cases.<sup>[4]</sup> Our patient had an early onset of disease with strongly positive autoantibodies to CFH. Autoantibodies to CFH prevent cell surface protection by CFH, chiefly by inhibiting binding to C3b. Low C3 levels are hence often demonstrated in this autoimmune variant of the disease.

aHUS may be suspected in patients with typical history along with proven negative stool cultures for Shiga-like toxin and normal ADAMTS13 activity and can be confirmed by genetic assays, though empiric treatment is often initiated. The autoimmune variant, however, as in our case may not have a genetic focus and can be diagnosed by high levels of antibodies to CFH (2043 AU/ml in our case). The overall aHUS has incomplete penetrance, and an infectious trigger is often associated with the disease precipitating.<sup>[5]</sup> Our case presented with a high-grade fever of undocumented etiology which was probably the trigger for complement activation.

Globally, eculizumab, the monoclonal antibody to C5b, has found acceptance in the treatment of aHUS.<sup>[6]</sup> The limiting factor is the cost of eculizumab therapy, especially in developing countries. Plasma exchange had been the gold standard in the treatment of aHUS before eculizumab. Guidelines issued in 2009 recommended initial daily plasma exchange (50–70 ml/kg) with further titration of frequency according to clinical response.<sup>[7]</sup> Our patient received an initial seven cycles of daily plasma exchange followed by gradual tapering with monitoring of hematological and renal parameters which showed complete normalization by the 12<sup>th</sup> cycle. Further, four cycles were continued till antibodies to CFH were almost undetectable. CFH-related aHUS, similar to



**Figure 2:** Skin lesions of Steven–Johnson syndrome with oral mucosal involvement.

our patient, has been documented to respond better to plasma exchange.<sup>[8]</sup> Our patient did not develop any requirement for renal replacement therapy with hemodialysis as is the norm in a majority of cases of aHUS. This can be attributed to rapid initiation of plasma exchange.

Hypertension is a common complication of aHUS but developed late in the course of treatment in our patient. Seizures are the most common neurological involvement in aHUS. Posterior reversible encephalopathy with associated loss of vision may have an identical presentation as cerebral thrombotic microangiopathy. The latter can be differentiated on the basis of asymmetry of the lesions on MRI.<sup>[9]</sup> Although neurological sequelae respond best to eculizumab, our patient was already in remission at the time of onset. His symptoms resolved with control of blood pressure. Steven–Johnson syndrome was probably a coincidental reaction to phenytoin and does not relate to aHUS in the available literature.

Cyclophosphamide, mycophenolate mofetil, azathioprine and steroids, all have supporting literature for maintenance therapy.<sup>[10]</sup> We chose azathioprine in view of relative ease of dosing.

The prognosis of aHUS remains guarded. In patients with CFH autoantibodies 36.5%–63% progress to mortality or end-stage renal disease in the long-term.<sup>[2,5]</sup> Our patient remains in clinical remission at 6 months on follow-up.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

#### REFERENCES

1. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med* 2009;361:1676-87.
2. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Ngo S, *et al.* Genetics and outcome of atypical hemolytic uremic syndrome: A nationwide French series comparing children and adults. *Clin J Am Soc Nephrol* 2013;8:554-62.
3. Kavanagh D, Goodship TH, Richards A. Atypical hemolytic uremic syndrome. *Semin Nephrol* 2013;33:508-30.
4. Hofer J, Janecke AR, Zimmerhackl LB, Riedl M, Rosales A, Giner T, *et al.* Complement factor H-related protein 1 deficiency and factor H antibodies in pediatric patients with atypical hemolytic uremic syndrome. *Clin J Am Soc Nephrol* 2013;8:407-15.
5. Kavanagh D, Goodship T. Genetics and complement in atypical HUS. *Pediatr Nephrol* 2010;25:2431-42.
6. Wong EK, Goodship TH, Kavanagh D. Complement therapy in atypical haemolytic uraemic syndrome (aHUS). *Mol Immunol* 2013;56:199-212.
7. Taylor CM, Machin S, Wigmore SJ, Goodship TH; working party from the Renal Association, the British Committee for Standards in Haematology and the British Transplantation Society. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. *Br J Haematol* 2010;148:37-47.
8. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, *et al.* Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010;5:1844-59.
9. Gulleroglu K, Fidan K, Hançer VS, Bayrakci U, Baskin E, Soylemezoglu O. Neurologic involvement in atypical hemolytic uremic syndrome and successful treatment with eculizumab. *Pediatr Nephrol* 2013;28:827-30.
10. Loirat C, Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis* 2011;6:60.